I) Discussion on mode of action of combination of Ayurvedic medicines –

Patients from Group A received combination of oral Ayurvedic medicines (RG4) from the beginning of radiotherapy and continued till 3 months after completion of Radiotherapy. RG4 protocol was consisting of Mouktikayukta Kamdudha\textsuperscript{77}, Mauktikyukta praval panchamrut\textsuperscript{78}, Ananta vati\textsuperscript{79} and Yashtimadhu ghrut\textsuperscript{80}.

Mouktikayukta kamdudha is a herbomineral Ayurvedic medicine containing Guduchi (Tinospora cordifolia) sattva as a herbal content and mineral contents like Shankh bhasma (Conch shell), Shauktik bhasma (Pearl shell), Kapardika bhasma (Cowries), Praval bhasma (Coral), Maouktik bhasma (Mukta) and Gairik (Red Lumber Stone). Guduchi poseses Tikta Kashay Ras and Madhur Vipak. It had Rasayan, Agni deepan, Balya, Dahshamaka, Jwaraghna and Raktashodhak action. It pacifies three Doshas. Guduchi sattava which is the starch based preparation of Guduchi has additional cooling effect. All these properties of Guduchi are beneficial in Pitta dominant, Raktadushtikar and Agnimandya induced side effects of radiotherapy. Its Rasayan action is also beneficial in suppressed immune status in these patients. Gairik posseses Pittashamk properties due to Madhur ras, Madhur vipak and Sheeta Virya. Additionally it has Vishanashak property. Thus it minimizes pitta dominant side effects of radiotherapy like stomatitis, xerostomia etc in oral cavity cancer patients and eliminates toxins accumulated in the process of disease development and radiotherapy. Praval posseses Madhur, Amla, Kashay ras, Madhur Vipak and Sheet Virya. It is Pitta Kapha nashak and posseses Rasayan, Jwarhar, Raktapittanashak and Vishghna action which is beneficial in radiotherapy induced toxicities like stomatitis, xerostomia, excessive salivation, loss of taste and boosting up immunity.

\textsuperscript{77} Sharma HP Rasa Yoga Sagar Part -1, Krishnadas/Ayurved Series, pp 260
\textsuperscript{78} Sharma HP Rasa Yoga Sagar Part -2, Krishnadas/Ayurved Series, pp 93.
\textsuperscript{79} Bhavprakash Nighantu by Bhavmishra with Vidyodini Hindi Commentary by Shree Bramha Shankar Mishra and Shree Ruplalji Vaishlya, Chaukhamba Sanskrit Samsthan, (2002), 10\textsuperscript{th} Edition, Nighantu Bhag,pp 65
\textsuperscript{80} Bhavprakash Nighantu by Bhavmishra with Vidyodini Hindi Commentary by Shree Bramha Shankar Mishra and Shree Ruplalji Vaishlya, Chaukhamba Sanskrit Samsthan, (2002), 10\textsuperscript{th} Edition, Nighantu Bhag,pp 426
Being raktaprasadak it also helps in maintaining hemoglobin levels during the course of radiotherapy. Mouktik bhasma possess Madhur Kashay ras, Madhur Vipak, and Sheet Virya. By these virtues it is Tridoshashamak, Dahanashak and Balya. Radiotherapy induced stomatitis, xerostomia and loss of weight are thus well controlled by administration of Mouktik Bhasma. Combination of Shankh bhasma, Shauktika bhasma and Kaprdika Bhasma is mainly Pachak and Tridoshshamak. Thus it alleviates aruchi and chhardi by improving digestion. Nausea and loss of taste developed during course of radiotherapy is well controlled with this combination. The mineral products of this combination namely Praval, Shankha, Shauktika and Kapardika are mainly aquatic in nature and thus posses Jal mabhut dominance. Most of the contents of this combination are Prithvi and Jala Mahabhuta dominant, thus they reduce the heat (Ushna Guna) in the body. A mineral in the form of Gairik is Prithvi Mahabhut dominant. Hence this combination is beneficial in Tej Mahabhut dominant side effects of radiotherapy according to Vishesh Siddhant\textsuperscript{84}.

Mouktikayukta praval panchamrut is a combination of Shankh bhasma (Conch shell), Shauktik bhasma (Pearl shell), Kapardika bhasma (Cowries), Praval bhasma (Coral), and Mouktik bhasma (Mukta). Mode of action of these minerals in radiotherapy side effect is already discussed. Praval Panchamrut can be preperaed by triturating it either with Arkakshira or godugdha. As we were expecting cooling effect and pittashamka activity in this study, we had prepared Praval Panchamrut with triturating with Godugdha.

Ananta possese Tikta, Madhur ras, Madhur vipak and Sheet virya due to which it has Pittashamka, Raktprasadak and Dahsghamka properties. It is Tridoshshamak and Visghghna. These properties of ananta are beneficial in Pitta Raktadushtikar side effects of radiotherapy like stomatitis and xerostomia. Due to its Visghghna property it detoxifies accumulated Pitta Rakta dominant doshas during the course of radiotherapy. It minimizes excessive heat in Raktadhatu during radiotherapy.

Yashtimadhu has Madhur ras, Madhur vipak and Sheet virya. It is Guru and Snigdha in nature. It possesses Vat Pitta Shamak, Dah shamak, Kanthya, Varnya, Sandhaniya and Rasayan properties. Yashtimadhu is used in this study in the form of Sidhha Ghrut which enhances its properties and exhibits soothing effect. In view of these properties Yashtimadhu ghrut is beneficial in minimizing stomatitis, xerostomia and trismus when administered orally as well as used as a local application internally in oral cavity. In these forms Yashtimadhu Ghrut heals mouth ulcers, softens facial muscles which become rigid during course of radiotherapy and imparts soothing effect on throat.

II) Discussion on observations, results and statistical analysis

Discussion on Demographic data and its role in oral cancer patients undergoing radiotherapy.

Management of radiation induced side effects described above is a perpetual problem in giving radiotherapy in oral cancers. The allopathic modalities of management of side effects are rather peripheral, which include nutritional support, pain control, oral decontamination, palliation of dry mouth, control of bleeding, and cryotherapy. Attempts are also being made to treat patients with keratinocyte growth factor and anti-inflammatory agents.

However, the fact remains that there is no definitive medicine to treat side effects of radiation especially in oral cancer. In this respect, the study conducted and data presented here is very useful. The drugs used are non-toxic, easily palatable and not very expensive, and the effect appears to be quite significant. The study was carried out in 2 groups. Group A was study group of 30 patients who have received Ayurvedic treatment (RG4) during RT and thereafter for three months. Group B was the control group of 30 patients who had received radiotherapy as described earlier.

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Patients diagnosed with oral cavity cancers and underwent radiotherapy are mostly in-between age of 41 – 60 yrs. in both the groups. Male patients are more than female patients (twice in numbers). More than 80 % patients of oral cancer underwent radiotherapy were in lower socioeconomical group. These observations are due to the fact that middle aged males in lower socioeconomical class are more addicted to tobacco in various forms. Though tobacco consumption is also common in middle and upper socio-economical class the percentage of development of oral cavity cancer is comparatively low due to awareness about screening facilities and maintaining oral hygiene.

Tobacco is main concern while considering risk factors in oral cancers. More than 80 percent of patients in both the groups are addicted to either smokeless or smoked tobacco in one or other form. It is found that tobacco when consumed with alcohol can increase the risk of cancer of the oral cavity and their combined use has a multiplicative effect on risk. Moreover, those regions of the mouth which are more directly exposed to alcohol or tobacco are more likely to be affected by cancer than other regions. For squamous cell carcinomas alcohol and tobacco also appear to increase risk synergistically.

In our study patients who underwent surgery before radiotherapy are more than those who are directly subjected to radiotherapy depending upon the stage of the disease and age of the patient.

Equal distribution of patients was found in both the groups, treated with or without adjunct chemotherapy. The general impression in practice is that toxicity is enhanced by the use of concurrent chemotherapy. But it should be noted that addition of chemotherapy to radiotherapy has significantly increased the morbidity of treatment as well as the chance of initial tumour response and local control. A statistically significant improvement in survival was found for the simultaneous use of chemotherapy and radiotherapy as per study done by Jay S. Cooper, Thomas F. Pajak, Arlene A. Forastiere etal on postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck 86.

Discussion on adverse effects of radiotherapy in oral cancer patients undergoing radiotherapy -

Stomatitis (Mukhapak) is a significant side effect of radiotherapy when given in oral cavity cancers. Radiotherapy hampers function of bodhak kapha which is present in oral cavity. It produces pitta and rakta dushti and thus induces mukhapaka.

It can be seen that in Group A (Study group) 15 patients had Grade I and II stomatitis immediately at the end of RT while 20 patients from group B (Control group) had grade III and IV stomatitis. It implies grade III and IV reactions were evident in control group patients while I and II reactions were seen in patients treated with adjunct Ayurvedic treatment. This observation statistically supported with significant p value ie p=0.025.

11 patients from group A were free of stomatitis while 2 patients from group B were free of stomatitis when assessed after 1 month of RT. At this time point 17 patients from group B and 12 patients from group A had grade II stomatitis. As radiotherapy side effects like stomatitis are remarkably reduced after completing radiotherapy grade III and IV stomatitis was persistent in very few patients as compared to grade I and II stomatitis. P value of stomatitis after 1 month of RT is also significant ie p= 0.019.

It is a common observation that severity of stomatitis is markedly reduced when observed after 3 months of RT. Our study also followed the same pattern. Thus very few patients suffered from grade III and IV stomatitis at this time point. When stomatitis was assessed 3 months after completing RT, 15 patients from group A were free of stomatitis while 6 patients from group B did not have stomatitis. At this time point 18 patients from group B and 12 patients from group A had grade II stomatitis. P value is also significant at this time point ie p= 0.022.

These observations established the efficacy of Ayurvedic treatment in management of stomatitis (Mukhapaka) which is caused due to pittavrudhi and Raktadushti as a consequence of radiotherapy.

Xerostomia meaning dryness of mouth due to reduced salivation is another common ill-effect of radiotherapy. Bodhak Kapha whose site is Mukha (oral cavity), is responsible
for salivation and thus keeping oral cavity moist. Radiotherapy which produces ushna guna, causes Bodhaka Kapha and Pitta dushti leading to dryness of mouth i.e. xerostomia.

In our study, 25 patients who were treated with adjunct Ayurvedic treatment and 8 patients who were treated with RT alone, did not develop xerostomia immediately after completing RT. On the other hand, 19 patients from control group developed grade IV xerostomia and only 1 patient from study group developed grade IV xerostomia at the end of RT. p value at this time point is thus extremely significant (p<0.001) indicating effectiveness of selected Ayurvedic medicines in minimizing ushna guna, pacifying bodhaka kapha and pitta dushti and thus subsiding xerostomia.

Xerostomia is usually a late side-effect of radiotherapy which continues years together after completing RT. In our study when patients were assessed till 3 months, it is observed that number of patients suffering from grade II and III xerostomia were significantly more after 3 months as compared to 1 month in control group. But this difference was not significant in study group, indicating efficacy of selected Ayurvedic medicines in alleviating xerostomia. This observation is also supported by highly significant p value (p=0.002), one month after completing RT and significant (0.001), three months after completing RT.

Radiotherapy induced loss of taste in oral cavity cancers is developed due to inactivity of taste buds as per modern medicine. According to Ayurvedic principles, Bodhaka Bapha, whose site is Jivha, is responsible for knowledge of tastes. Radiotherapy which hampers functions of bodhaka Kapha, causes loss of taste.

In our study, selected Ayurvedic medicines were not found to be effective in both groups. Perhaps it may be due to physiological irreversible changes in taste buds after radiotherapy.

Radiotherapy induced excessive salivation is caused due to Aashayapakarshagati of prakupita Vatadosha, which is vitiated due to excessive dryness produced during radiotherapy. Prakupita Vatadosha carries Kaphadosha at oral cavity, producing excessive salivation.
In our study, 28 patients from study group did not develop excessive salivation while 23 patients from control group did not suffer from excessive salivation, immediately after completing RT. At the same time grade III excessive salivation was developed in 4 patients in control group and none of the patients from study group developed grade III excessive salivation.

Radiotherapy induced trismus is developed due to aggravated ruksha and laghuguna of Vatadosha during the course of radiotherapy.

Ayurvedic medicines, mainly Yashtimadhu ghruta (used for oral administration and local application) was effective in alleviating ruksha guna of vatadosha and subsequently maintaining softness of muscles of oral cavity. This process helps to prevent trismus.

This expected mode of action of Ayurvedic medicine was proved in our study. More than half of the patients in study group did not develop trismus at all 3 time points, while half of the patients from control group developed grade IV trismus immediately after completing RT. Statistically extremely significant results were found at all three time points.

Radiotherapy induced dysphagia is mainly developed during the course of radiotherapy as a consequence of stomatitis. This symptom remains persistent, but with less severity, after completing RT due to xerostomia.

In our study, dysphagia was statistically very significant (p= 0.004) immediately after completing RT. This was due to the fact that stomatitis was well controlled by selected Ayurvedic medicines.

Nausea is a less common side-effect of radiotherapy in oral cavity cancers. It is developed mainly due to loss of taste and occasionally due to hampered digestion.

In our study, very few patients from both the groups develop nausea during and after radiotherapy and thus statistically it was not significant.
Weight loss is a frequently occurring side-effect of radiotherapy in oral cavity cancer patients due to inability to take food. It is developed due to stomatitis, trismus, xerostomia, dysphagia and nausea. This symptom is obvious during the course of radiotherapy, while remarkable weight gain is observed within few weeks after completing RT.

In our study weight loss was observed in nearly all patients in both the groups. Thus statistically it was not significant (p=0.16, 0.37 and 0.56) respectively at 3 time points.

**Discussion on Karnofsky score and Scores of QoL -**

In this study, we assessed the patient’s response to treatment in terms of functional ability and global status with the help of QLQ of EORTC and karnofsky scores which are well-accepted methods of analysis of outcome measures.

Karnofsky score for performance status was recorded for assessment of general wellbeing and ability to conduct activities of daily life. The higher score of Karnofsky denotes better ability to carry on normal activity which was recorded in Oxford Textbook of Palliative Medicine. As karnofsky score indicates feeling of wellbeing. It commonly shows decreasing trend during the course of RT. As per this trend karnofsky score of most of the patients in control group was not improved during the course of RT and 1 and 3 months after completing RT (21, 18, and 18 respectively). On the other hand karnofsky score was either maintained or improved immediately after RT in study group (23, 6 respectively). Same pattern of karnofsky score is observed when compared on 1 and 3 Months after completing of RT in this group. Our results showed increase in karnofsky score is maintained at the end of radiotherapy while it is steadily increasing after 1 month of RT and after 3 months of RT in group A, indicative of beneficial effects of adjunct oral Ayurvedic medicines. On the other hand, remarkable decrease in karnofsky score is noted in group B patients, during RT and 1 month after RT.

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Karnofsky score shows $p<0.0001$ (extremely significant), $p=0.0019$ (very significant) and $p=0.0004$ (extremely significant) when tested immediately after RT, after 1 month of RT and after 3 months of completing RT.

The Quality of Life (QLQ) is assessed on the basis of 3 parameters ie functional score, global score and symptom score as per EORTC QLQ - C30. Symptom score specifying symptoms of head and neck cancer were also noted by QLQ - H & N 35. Functional scale is the sum total of improvement in all ill effects of radiotherapy leading to achieving normal levels of functional ability of the patient, which is end point of assessment of well – being of the patient. It is a numerical score. Increase in the score denotes improvement in general functional activity of the patient. Global score denotes improvement in QLQ as judged by the patient himself. Head and neck symptom score is total score derived from specially designed questionnaire specifically in view of symptoms of oral cancer. Higher score indicates severe symptom gradations. Functional score and Global score of QoL is normally hampered after completing RT and this process continues for next few months due to long lasting side effects of RT. In our study decreased functional and global scores were observed in almost all patients in control group, while these parameters are improved or maintained in nearly 2/3 patients of study group. This indicates effectiveness of selective Ayurvedic medicines in boosting immunity due to their rasayan action, decreasing symptomatology and ultimately improving functional ability of patients during and after RT. Functional score and global score were significant at all time points when tested.

Symptom score is the sum total effect of all the symptomatic parameters. Decrease in symptom score indicates well being of patients. In our study symptom score reflected disease related symptoms like pain, trismus etc and symptoms of side effects of radiotherapy like xerostomia, stomatitis. Thus this score is more evident immediately after completing RT. Efficacy of Ayurvedic treatment on management of disease related and radiotherapy side effects related symptoms is proved in our study with the fact that symptom score was not improved in none of the patient in control group immediately after completeing RT, on the other hand it is improved or maintained in 23 patients of group A. This is due to the fact that disease related symptoms and radiotherapy related symptoms were well controlled by combination of radiotherapy and Ayurvedic treatment.
Symptom score shows p<0.0001 (Extremely significant), p= 0.434 (not quite significant) and p= 0.051(not quite significant) when tested immediately after RT, after 1 month of RT and after 3 months of completing RT respectively. This is due to the fact that all radiotherapy side effects in oral cavity cancer are evident during the course of RT and gradually subside within few weeks of completion of RT.

Head and Neck symptom score represents symptoms related to disease and symptom related radiotherapy side effects. It is peculiarity of radiotherapy in oral cavity cancer that the side effects related symptoms are more or less similar to that of disease related symptoms. Thus these symptoms are aggravated during course of RT. Symptom score of H&N 35 questionnaire represents sum total of both these symptoms. It is noticeable that score of these symptoms is improved (Reduction in total symptoms) in more than 20 patients at all three time points in group A, while H & N is not improved (symptoms aggravated) in 20, 21 and 15 patients at three time points respectively in group B. This indicates head and cancer related and RT side effects related symptoms were well controlled with combination of RT and Ayurvedic treatment. When Head and neck symptom score is considered it shows decreasing trend in control group patients that is (74-81-81-76) at four time points respectively while it represents decreasing trend in study group ( 76-71-70-65) at respective time points. This observation is supported by statistical evaluation with extremely significant p<0.0001 (extremely significant) at end of RT, p= 0.002 (significant) after 1 month of RT and p=0.061 (Not significant) after 3 months of RT.

These findings suggest that all scores of QLQ are also highly significant immediately after RT and for functional score and global score till three months of RT. Assessment of radiation induced symptoms described above was done by clinicians (as per CTC guidelines). As per QLQ guidelines these symptoms were also assessed by patients in their own perspective and recorded as symptom score of QLQ. It was interesting to note that both the assessments matched. All the scores show significant improvement in patients treated with adjunct oral Ayurvedic medicines.